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Review

Current status of the therapeutic uses and actions of the preferential cyclo-oxygenase-2 NSAID, nimesulide

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Abstract. This review summarizes the principal therapeutic responses to the preferential COX-2 NSAID, nimesulide, in treating musculo-skeletal joint symptoms and various acute and chronic pain conditions and the mode of action in relation to therapy in these states.

In extensive studies in laboratory animal models and clinical trails in patients nimesulide has been found to have potent analgesic, anti-inflammatory and anti-pyretic activities. It is approved for use in over 50 countries worldwide (including those in the EU, South and Central America, China, India and some other South-East Asia) for the treatment of acute pain, the symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. Its mode of action in these states is related to the preferential inhibition of the production of cyclo-oxygenase-2 (COX-2) and other inflammatory mediators whose production is controlled by stimulation of cyclic-3 ,5´-adenosine monophosphate (cAMP); this means that nimesulide is a multi-factorial drug in controlling inflammation and pain.

The adverse reaction profile of nimesulide is, in general, like that of other NSAIDs. It does, however, have relatively low occurrence of gastro-intestinal (GI) side effects which is related to its low propensity to inhibit the physiologically important COX-1 in the GI mucosa and important physicochemical properties (high pKa of 6.5 and lipohilicity) as well as inhibiting of mast cell derived histamine and acid secretion in the stomach. In contrast with the coxibs, nimesulide has not been found to have appreciable cardiovascular toxicity.

Key words: NSAID; Anti-inflammatory; Analgesic; Side-effects; Sulphonanilide; Cyclooxygenase

Introduction

It is well-established that non-steroidal anti-inflammatory drugs (NSAIDs) have fundamental actions in controlling inflammation and in pain relief (Kean and Buchanan, 2005). They all inhibit the production of prostaglandins through the inhibition of COX-1 and COX-2, these being the enzymes responsible for their synthesis (Vane and Botting, 2001; Rainsford, 2004a). In addition, however studies in experimental and clinical models have clearly demonstrated other activities on pro-inflammatory mediators involved in the actions of NSAIDs in providing relief from inflammation and pain (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Celotti and Laufer, 2001; Tarnawski and Jones, 2003; Rainsford, 2004;). Among these mechanisms are the inhibition of leucocyte accumulation at inflamed sites, activation and expression of cell surface receptors, of angiogenesis, cell apoptosis, reactive oxygen species (ROS, or oxyradicals and nitric oxide) and their actions, and the regulation of non-prostanoid lipid mediators (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Tarnawski and Jones, 2003; Rainsford 2004a, 2004b; Celotti and Laufer, 2001; Serhan, 2004)

Aside from individual variations in pharmacological effects NSAIDs also differ substantially in the pharmacokinetic, pharmacological, pharmacodynamic and in their clinical profiles (Hart and Huskisson, 1984; Brogden, 1986; Bannwarth et al., 1989; Levy and Smith, 1989; Netter et al., 1993; Evans, 1996; Hayball, 1996; Rainsford, 1996; Lefkowith 1999; Heyneman et al., 2000; Verbeeck 1990; Celotti and Laufer, 2001; Day 2001; Landoni snd Scoraci, 2001; Bijlsma 2002; Tarnawski and Jones, 2003; Rainsford et al., 2005a, 2005b; Huntjens et al., 2005). Since they have essentially the same therapeutic properties in controlling pain, inflammation and fever, the scale of adverse effects often remains the main discriminator for choosing between individual NSAID (Hart and Huskisson, 1984; Rainsford, 1996; Kean and Buchanan, 2005).

Gastrointestinal (GI) adverse events remain the main concern in the use of NSAIDs and GI tolerability is a central issue for clinicians who prescribe these drugs (Rainsford, 1996, 2001; Rothstein, 1998). Other important side effects should also be taken into consideration when prescribing these drugs such as allergic reactions, skin adverse reaction, renal complications, alteration of hepatic enzyme levels and rarely hepatopathies (Rainsford, 1996, 1997, 2001; Rothstein, 1998; Teoh and Farrell, 2003; Uemura et al., 2003; Simon and Namazy, 2003; Sanchez-Borges et al., 2002, 2003; McGettigan et al., 2000).

Finally, the recent withdrawal of two of the newer COX-2 selective NSAIDs, rofecoxib and valdecoxib because of serious cardiovascular reactions (the latter also due to serious skin reactions), as well as the withdrawal or limitations on the use of celecoxib in some countries poses question about the cardiovascular (CV) safety profile of the whole NSAIDs class (Rainsford, 2005c; Khanna et al., 2005; Oster and Hazleman, 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). The FDA and EMEA took different positions on this issue. The FDA took the view that the issue concerning the CV risks of coxibs raised concerns about the CV safety of all NSAIDs (US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). In contrast, the EMA considered the CV risk of coxibs was clearly greater than that of other NSAIDs whether preferential or non-selective COX-2 inhibitors (which they grouped as non-selective COX-2 inhibitors) (European Medicines Agency, 2005a, 2005b).

Traditional NSAIDs and selective COX-2 inhibitors

In 1971, Professor Sir John Vane and colleagues postulated that aspirin and other NSAIDs, produced their anti-inflammatory and analgesic effects by inhibiting the biosynthesis of prostaglandins, through the blockade of the COX enzyme (Vane, 1971; Ferreira et al., 1971; Flower et al., 1972). In the early 1990's, it became evident that two isoforms of the COX enzyme were actually involved in the production of prostaglandins (Rainsford, 2004a, Vane and Botting, 1995, 2001). In particular, it was showed that the COX-1 isoform is responsible for the production of prostaglandins which contribute to maintain the homeostasis in key organs such as the stomach and kidney as well as influence mechanisms linked to the blood coagulation and vascular functions. The other isoform, COX-2, was found to be mainly induced by inflammatory and painful stimuli and to cause the formation of prostaglandins which play a key role in the inflammation and neural responses, although more recent research attributes a role in the maintenance of homeostasis to this isoform as well (Vane and Botting, 1995, 2001; Rainsford, 2004a).

Non-selective NSAIDs inhibit both COX-1 and COX-2 by binding reversibly or irreversibly to the enzyme (Vane and Botting, 1995; Rainsford, 2004a. The toxic effects of these non-selective NSAIDs in the gastro-intestinal tract, kidney and vascular systems are considered, in part, to be due to inhibition of the synthesis of physiologically important ("housekeeping") prostaglandins (PGs) E_2 and I_2 in these systems (Vane and Botting, 1995, 2001; Rainsford, 2004a). Inhibition of COX-2 selectively inhibits the synthesis of PGE_2 and other PGs involved in inflammation and mediating neural signals in pain pathways Vane and Botting, 1995, 2001; Rainsford 2004a, 2004b; Rainsford et al., 2005). NSAIDs exhibit different degrees of selectivity in their ability to differentially block COX-1 or COX-2 (Vane and Botting, 1995, 2001; Rainsford, 2004a; Tarnawski and Jones, 2003). While there are many other factors that are involved in the development of adverse reactions (e.g. in the GI tract and kidney) the involvement of COX-1 inhibition plays a significant part (Rainsford, 1996, 2001; Hotz-Behofsits et al., 2003; Tarnawski and Jones, 2003).

In late '90s based on the assumption that the inhibition of COX-1 is the main cause of GI bleeding, a new class of highly selective COX-2 inhibitors, the so-called coxibs, were developed (de Laval et al., 2000; Vane and Botting, 2001; Rainsford, 2004a). Their purpose was to inhibit, at recommended therapeutic doses, mainly COX-2, with little if any effects on COX-1 (Vane and Botting, 2001; Rainsford, 2004a). The coxibs were, therefore, looked at as a safer alternative to traditional NSAIDs, especially their GI safety profile. Evidence from short-term studies showed that the coxibs had lower gastro-ulcerogenic effects in animals and humans (Feldman and McMahon, 2000). Since their discovery certain physicochemical properties (high pKa, lipophilicity) have been identified that may also account for their low acute GI ulcerogenicity (Rainsford, 1999a). In long-term studies in patients with arthritic conditions this was less marked and the incidence of serious GI events from coxibs proved similar to that from NSAIDs (Bjarnason and Rainsford, 2001a, 2001b; Schoenfeld, 2001; Jüni et al., 2002).

The inhibitory activity of NSAIDs towards the two COX isoforms is only one of the aspects which play a role in their analgesic and anti-inflammatory activity. Aside from the degree of selectivity toward COX isoforms, NSAIDs can be distinguished according to other characteristics such as their chemical structure, as well as their acidic and non-acidic chemical characteristics (e.g. pKa) (Rainsford, 1999a, 2004c). Their biological activities are also due to their relative effects on the production of inflammatory and pain mediators which account for their anti-inflammatory, analgesic activities (i.e. central or peripheral) antipyretic and other pharmacological properties. Physico-chemical factors are well-known to influence pharmacokinetics of NSAIDs (Graf et al., 1975; Brune et al., 1977; Netter et al, 1993) and especially the rate of GI absorption and uptake into inflamed cells or synovial tissues and cerebrospinal fluids (Netter et al., 1993; Rainsford, 1999a, 2004c; Shimizu et al., 2003; Pehourcq et al., 2004;). NSAIDs with low pKa values (e.g. carboxylic acids) have a greater tendency to be irritant to the gastric mucosa as a consequence of their selective absorption into GI mucosal cells (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Hotz-Behofsits et al., 2003; Rainsford, 1999a; Sigthorsson et al, 2000a, 2000b) leading to ion trapping (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Sigthorsson et al., 2000), as well as uptake into mitochondria and

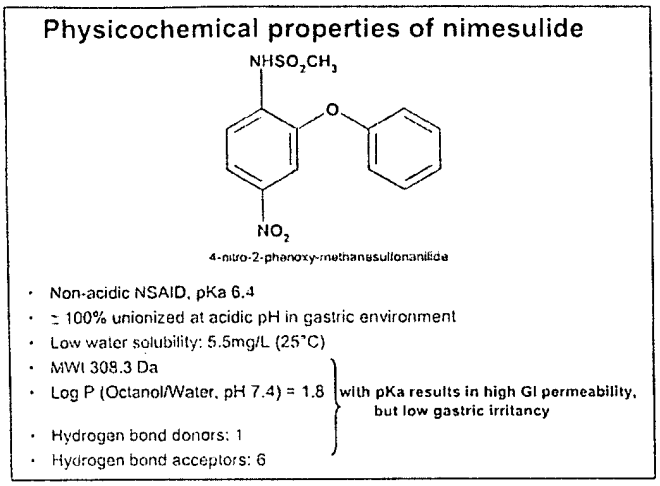

Fig. 1. Physico-chemical properties of nimesulide.
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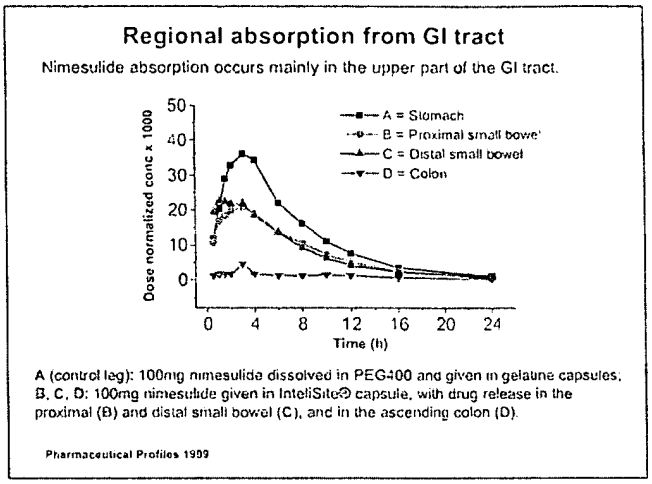

Fig. 2. Plasma concentrations of nimesulide normalized to dose following selective introduction into different regions of the gastro-intestinal tract. These data show that about 70% of the dose of the drug taken orally is absorbed in the stomach, while about 12% is absorbed in the small bowel and virtually no absorption occurs in the colon.

uncoupling of oxidative phosphorylation (Sigthorsson et al., 2000) leading to reduction in ATP production and apoptosis (Redlak et al., 2005). These physicochemical features of NSAIDs also underlie their renal effects (Brune et al., 1977). Drugs with relatively higher pKa than the carboxylates such as nimesulide (pKa 6.5) (Fig. 1) while being well absorbed probably have a lower propensity to lead to ion trapping in mucosal cells (Rainsford, 1999a; Sigthorsson et al., 2000) and consequently are less irritant to the mucosal cells (see later section on Adverse Reactions and Relative Safety).

The Development of Nimesulide

Nimesulide was developed by Dr. George Moore and colleagues at Riker Laboratories (later acquired by 3M Co.) (Rainsford, 2005a). The discovery of nimesulide preceded the discovery of cyclo-oxygenase and the key roles of prostaglandins in inflammation and pain. The rationale for the design was actually based on the premise that free radicals were critical factors in chronic inflammation disease and scavenging of these radicals might have novel anti-inflammatory activities in the control of chronic inflammatory conditions (Swingle et al., 1985; Rainsford, 2005a).

Following initial unsuccessful observations on fluoroalkane-sulfonanilides they modified their strategy to incorporate a 4-nitro- group into the sulphonanilide structure to achieve oxyradical scavenging and this led to the synthesis of 4- nitro-2-phenoxy-trifluoromethane-sulfonanilide. The designated compound, R-805, was found to have the best therapeutic ratio compared with reference NSAIDs available at that time (Rainsford, 2005a). The chemical name of the compound, 4-**nitro**-2-phenoxy**methane**-**sulphonanilide** served as the basis for the generic name of the drug, i.e. nimesulide. Subsequently in 1980 nimesulide was licensed by Helsinn Healthcare SA (Switzerland) who proceeded to invest in extensive investigations on the drug. These gave a basis for comprehensive investigations that allowed for the worldwide registration and commercialisation of the drug. These studies also led to identification of the multi-factorial basis for the actions of nimesulide.

Nimesulide was first licensed and marketing in Italy in 1985, over 20 years ago. Subsequently, it has become the most prescribed and used NSAID in that country. It is now marketed in over 50 countries world-wide and in some is amongst, if not, a market leader.

Mode of Action of Nimesulide

There have been several reviews published over the years on the pharmacological properties of nimesulide (Ward and Brogden, 1988; Davis and Brogden, 1994; Famaey, 1997; *Anonymous*, 1998; Bennett and Villa, 2000; Bennett, 2001). More recently, a monograph has been published on nimesulide which includes all the main pharmacokinetic, pharmacological, clinical and chemical properties of this drug (Rainsford, 2005b).

Pharmacokinetics

Key features of the pharmacokinetics of nimesulide, which are important in relation to its pharmacological actions, include:

- Rapid and complete absorption from the upper gastro-intestinal tract (Fig. 2); peak plasma concentrations ranging from 3–6.5 mg/L being reached at 1–3 h after oral ingestion of the recommended daily dose of 100 mg b.i.d. (Bernareggi,1998; Bernareggi and Rainsford, 2005).
- Tissue distribution in rats (Fig. 3) shows rapid accumulation in fat, liver, kidney, with some uptake into brain tissue in rats. High fractional binding of the drug and its principal 4-hydroxy-metabolite to plasma proteins, principally albumin, ensures moderately low volume of distribution with V_z/F = 0.2 to 0.4 L/Kg (Bernareggi, 1998; Bernareggi and Rainsford, 2005a). Clearance is rapid such that most of the drug is eliminated in rats and humans by 24 h (Bernareggi, 1998; Bernareggi and Rainsford, 2005).

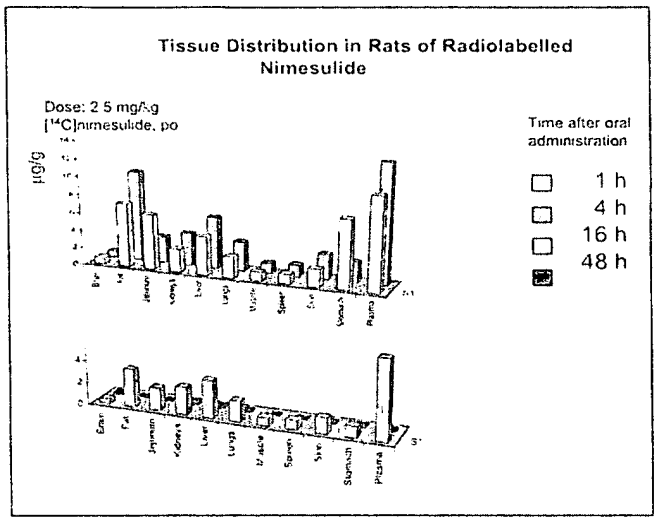

Fig. 3. Distribution in major organs of radioactive labelled-nimesulide in rats following oral administration of 2.5 mg/kg of the drug.
The upper bar graph shows the concentration (µg/g wet weight) of nimesulide and its principle 4-hydroxy-metabolite at 1 h (front bars) and 4 h (at rear), while the bottom graph shows the concentration of these at 16 h (front bars) and 24 h (at rear) respectively.
There is widespread distribution of radioactively labelled drug within 1 h of oral administration with relatively high concentrations being present in the plasma, fat, stomach, jejunem, liver, kidneys and lungs. The presence in fat reflects the relatively high liposolubility of the drug. Although there is some uptake into the brain at 1–16 h this is not at a high level compared with the plasma concentration of the drug. The combined tissue to plasma ratio is <1 and there is no accumulation of the drug in major organs. In humans the ratios of tissue/plasma drug concentrations in synovial and genital tissues are in the range of 0.4–0.8. Figures derived from data in [illegible] and A. Bern[illegible] (1991). Disposition of total radioactivity and plasma levels of nimesulide and OH-nimesulide in rats after intravenous and oral administration. Data on file – Helsinn Healthcare S.A.

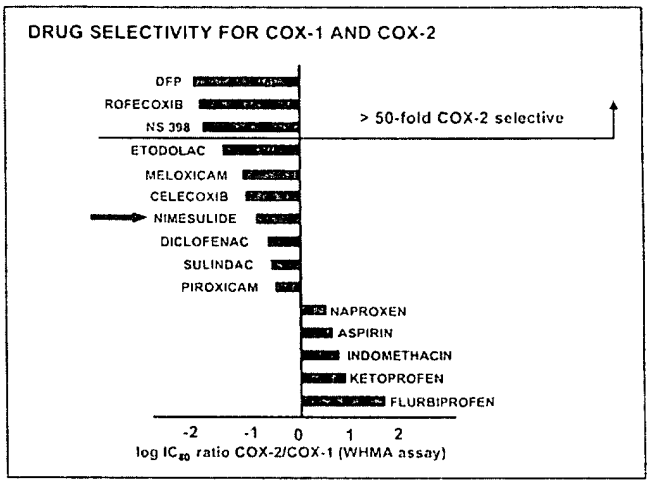

Fig. 4. *In vitro* selectivity of NSAIDs for COX-2 compared with COX-1. Based on data from Warner et al. (1999). Here there IC_{50} molar values for the inhibition of these two enzymes are compared as this is considered to give a closer representation of the likely effects in relation to the plasma concentrations of the drugs in humans.

- There is similar bioequivalence from different oral dosage forms (tablets, granules, suspension) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Food has a modest effect on total bioavailability; a relatively high fat American breakfast reducing peak plasma concentrations (C_{max}) by about 20% but there is no effect on the T_{max} or total bioavailability (AUC_{0-15hr}) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Liver metabolism is principally due to (a) oxidation to form hydroxylated metabolites via cytochrome P_{450} 2C9, 2C19 and possibly CYP1A2, with subsequent glucuronidation and sulphation of the phenolic hydroxyl groups, and (b) reduction of the nitro-group to an amine (Bernareggi, 1998; Bernareggi and Rainsford, 2005). Nitroso- and hydroxylamine intermediates most likely occur in the reduction of the nitro-group (Bernareggi and Rainsford, 2005).

While nimesulide produces a considerable number of metabolites, the principal metabolite is the 4-hydroxy-derivative which, though generally less potent, has similar pharmacological actions to that of the parent drug (Rainsford et

COX-2 and anti-inflammatory activity

A large number of experimental investigations in animal models (Rainsford et al., 2005) and humans with arthritic and various pain states (Bianchi et al., 2005) have shown that nimesulide has anti-inflammatory activity which is comparable on a dose for weight basis with that of conventional NSAIDs such as diclofenac and indomethacin and the COX-2 selective drug, rofecoxib.

The effects of nimesulide, like that of other NSAIDs on COX-2 are among the mechanisms involved in the anti-inflammatory actions of this drug. The preferential COX-2 selectivity of nimesulide is a central feature of the anti-inflammatory as well as analgesic effects of this drug (Rainsford et al., 2005). Demonstration of this effect has been shown in a conventional *in vitro* and *ex vivo* assays. Among the *in vitro* assays used to define COX-1 and COX-2 selectivity of NSAIDs that developed by Warner and co-workers (Warner et al., 1999), known as the William Harvey (Institute) Modified Assay (WHMA) in whole human blood (Fig. 4) has become generally accepted to most closely represent that known to occur *in vivo* and best characterized in relation to the plasma pharmacokinetics of the drugs. The ratio of COX-2/COX-1 (which is a measure of COX-2 selectivity) in the WHMA data was found to range between diclofenac and etodolac and was close to that of celecoxib (Fig. 4). Yet the COX-2/COX-1 ratio of nimesulide is clearly out of the range of rofecoxib and NS-398, both of which are highly selective inhibitors.

To establish the significance of COX-2 selectivity in relation to GI effects and platelet function *ex vivo* studies were performed in human volunteers who had ingested either 100 mg nimesulide b.i.d. or naproxen 500 mg b.i.d. for 14 days and the COX-1/COX-2 effects were determined in blood and GI mucosa. There was no COX-1 – dependent platelet aggregation produced by nimesulide and it only

(TxA_2) and gastric mucosal production of PGE_2 and 6-keto $PGF_{1\alpha}$ in endoscopic biopsies (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000a, 2000b; Shah et al., 2001). Whole blood stimulated ex vivo with *Escherichia coli* lipopolysaccharide (LPS) from the nimesulide-treated subjects produced 91–93% inhibition of PGE_2 compared with control values after 3–10 days treatment.

In comparison, the ingestion of naproxen 500 mg b.i.d. for 14 days caused significant reduction in serum TxB_2 production (by 98% of initial control values), gastric mucosal PG production by 76–82%, and blocked COX-1 dependent platelet aggregation. The LPS-stimulated whole blood PGE_2 production was significantly reduced by 74–77% of control values over 3–10 days *ex vivo*; the latter being less than that observed with nimesulide (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001;).

The significance of these observations on COX-2 preferential effects of nimesulide on the gastro-intestinal (GI) effects of the drug were shown in upper GI endoscopic observations performed in the same volunteers and parallel studies of intestinal permeability using specific biomarkers. In both studies nimesulide had little or no effects on the Lanza scores of gastro-duodenal mucosa or intestinal permeability whereas naproxen produced significant gastric injury (44% of subjects showing >10 erosions or haemorrhagic areas) and increased intestinal permeability. Furthermore, naproxen caused a significant two-fold increase in excretion of faecal calprotectin (a marker of intestinal inflammation) above baseline whereas nimesulide was without significant effects on the excretion of this biomarker (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001).

These results represented the first conclusive evidence of COX-2 selectivity of an NSAID being paralleled in humans by lack of significant effects on GI mucosal integrity. These observations are supported by a large amount of studies in laboratory animal models (Sigthorsson et al., 2000) (reviewed – see Bjarnason et al., 2005; Rainsford et al., 2005) showing little or no effects of nimesulide on GI mucosal production of prostaglandins coincident with low GI mucosal injury from this drug.

Several actions of nimesulide may also account for the low GI ulcerogenicity of the drug aside from sparing of COX-1 activity in the mucosa and physico-chemical properties of the drug that limit its accumulation in mucosal cells (Bjarnasson et al., 2005). Among these actions are the effects on mast cell degranulation and release of histamine, and inhibition of histamine stimulated acid production which maybe a consequence of elevation of cyclic 3′5′-AMP by nimesulide (Bjarnasson et al., 2005) (see later). The lack of stress-synergy in expression of irritant actions of the drug on the gastric mucosa, such as seen with other NSAIDs may also be a factor of significance in the low ulcerogenicity of nimesulide (Rainsford, 1975, 1977).

The pharmacological profile of nimesulide with particular reference to its inhibitory activity on the COX enzymes, has been evaluated in various *in vitro* models. Although results vary depending on study conditions, nimesulide showed a higher affinity for the COX-2 enzyme (Rainsford et al., 2005). This is also supported by molecular modelling studies which showed that blockade of COX-2 is due to the

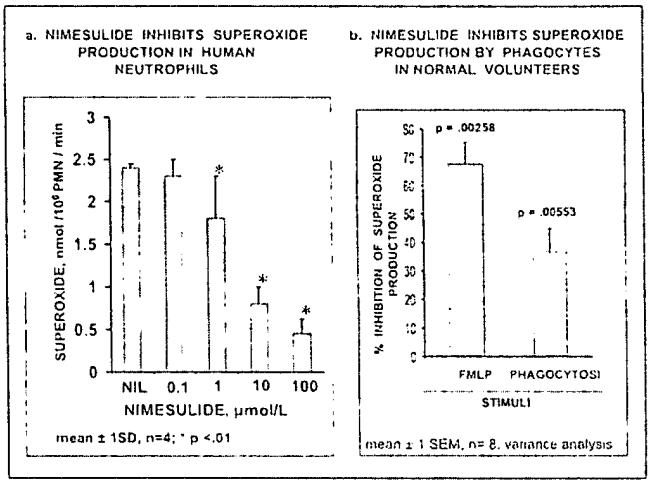

Fig. 5. Actions of nimesulide on neutrophil reactive oxygen species (ROS). Effects of nimesulide on superoxide production by human neutrophils *in vitro* (a) and on superoxide and phagocytosis by neutrophils ex vivo following ingestion by human volunteers of 100 mg nimesulide (b).

a. Based on data from Bevilacqua et al. (1994)

b. Based on data from Ottonello et al. (1992)

interaction of nimesulide with the larger channel in COX-2 compared with COX-1 (Rainsford et al., 2005) In these experimental models nimesulide was also found to have some weak inhibitory activity on the COX-1 isoform (Rainsford et al. 2005), which might have therapeutic advantages in relation to prevention of thrombosis in patients with atherosclerosis.

Nimesulide, like some classical NSAIDs exhibits a considerable degree of anti-inflammatory activity as a consequence of various inhibitory effects on polymorphonuclear neutrophil leucocytes (PMNs) (Dallegri et al., 1990, 1992a, 1992b, 1995; Ottonello et al., 1992, 1993, 1995, 1999; Capecchi et al., 1993; Verhoeven et al., 1993; Bevilacqua et al., 1994; Dapino et al., 1994; Tool and Verhoeven, 1995; Bennett and Villa, 2000; Bennett, 2001; Mouithys-Mickalad et al., 2000; Nakatani et al., 2001; Gomez-Gaviro et al., 2002; Bravo-Cuellar et al., 2003; Kimura et al., 2003; Rainsford et al., 2005). These effects are, in some cases, relatively potent compared with the activities of other NSAIDs, and occur within the drug concentrations in plasma or synovial fluids encountered during therapy with the drug (Rainsford et al., 2005; Bennett and Villa, 2000; Bennett, 2001). Thus, nimesulide inhibits chemotaxis and superoxide production at ≥1 µmol/L (Fig. 5) and production of platelet activating factor, leukotriene B_4 and hypochlorous acid (HOCl) from PMNs at ≥10 µmol/L in concentrated-related manner (Dallegri et al., 1990, 1992a, 1995; Ottonello et al., 1992, 1993,1995; Verhoeven et al., 1993; Bennett and Villa, 2000, Bennett 2001). At ≥5 µmol/L nimesulide inhibits release of elastase and other markers of neutrophil degranulation that contribute to cartilage destruction in osteoarthritis (OA) and related conditions (Ottonello et al., 1993; Nakatini et al., 2001). At higher "supra-therapeutic" concentrations (≥20 µmol/L) nimesulide inhibits neutrophil adherence to endothelial cells, shedding of L-selectin and transendothelial migration (Fig. 6) (Dapino et al., 1994; Gomez-Gaviro et al., 2002).

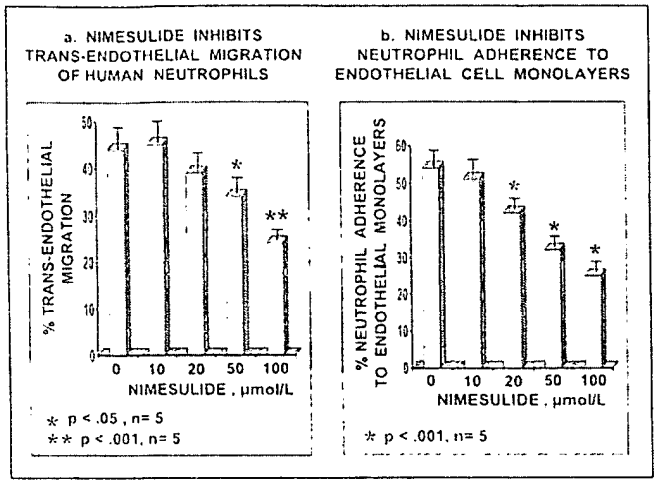

Fig. 6. Actions of nimesulide on neutrophil-endothelial cell interactions. Effects of nimesulide on the migration of neutrophils through endothelial cells (a) and on neutrophil adherence to endothelial cell monolayers (b).
a, b. Based on data from Dapino et al. (1994)

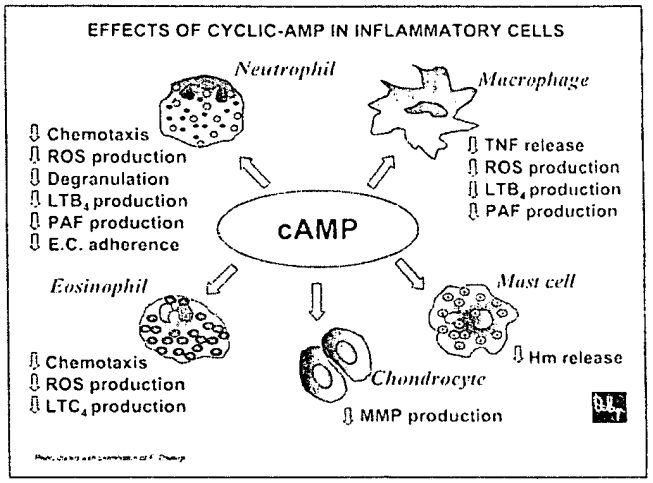

Fig. 7. The central actions on leucocytes, mast cells and chondrocytes of nimesulide as a consequence of regulation of cyclic-3′,5′-adenosine monophosphate (cAMP). It is postulated that as nimesulide increases production of cAMP as a consequence of inhibition of phosphodiesterase-IV; this increased cAMP leads to reduced production of a wide range of inflammatory mediators by neutrophils, macrophages, mast cells and eosinophils. The reduction via cAMP in the cytokine stimulated release as well and the direct effects on the activity of metalloproteinases (MMP) especially of stromelysin (MMP-3), MMP-1 and MMP-8 from chondrocytes (Barrachini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005).may, with the actions of nimesulide in activating glucocorticoid receptors, may contribute to reduced degradation of cartilage in osteoarthritis.
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Confirmation of the actions *in vivo* in humans of nimesulide on neutrophil oxidative reactions has been provide by Ottonello and co-workers (1992) who showed that oral ingestion of 100 mg nimesulide lowered the phagocytic superoxide generation of neutrophils in response to opsonized zymosan particles and *N*-formylmethionyl-leucyl-phenylalanine (Fig. 5).

In contrast to the effects on neutrophils, nimesulide (>0.1 µmol/L) reduces the survival of human monocytes suggesting that this drug may have selective actions on apoptosis or other actions that affect growth of monocytes (Sawada et al., 2000).

An important action of nimesulide not observed with many other NSAIDs is its ability to inhibit the release of histamine from mast cells (Casolaro et al., 1993; de Paulis et al., 1997; Kolaczkowska et al., 2002). This effect probably has significance not only in vasodilatation in acute inflammation but also for the wide range of actions of histamine now known to be of importance in chondrocytes and other cells involved in joint manifestations of arthritic diseases (Tanaka et al., 1997).

In addition to effects on mast cells, nimesulide inhibits chemotaxis and production of reactive oxygen species (ROS) and leukotriene C_4 production by eosinophils (Tool et al., 1996); these effects may be of significance in control by the drug in airways inflammation and allergic reactions although proof of the clinical effects is not yet available.

It has been postulated that a central or basic action of nimesulide in elevating intracellular levels of the key cell signal, cyclic 3′,5′-AMP (cAMP) may account for the wide-ranging inhibitory effects on inflammatory cells and release of cartilage degrading enzymes (e.g. matrix metalloproteinases) (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004). Figure 7 shows the central role that elevation of cAMP plays in mediating these actions. Confirmation of the effect of nimesulide on cAMP in PMNs has been shown in which the activity of the enzyme that degrades cAMP, phosphodiesterase IV, is inhibited at concentrations ≥1 µmol/L coincident with increase in intracellular cAMP. This increase causes activation of protein kinase A which leads to inhibition of the various functional responses shown in Figure 7.

The potential protective effects of nimesulide on cartilage-degradation may be due to inhibition of the activity and production of metalloproteinases (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), urokinase (Pelletier et al., 1997), expression of pro-inflammatory cytokines (Pelletier et al., 1997; Fahmi et al., 2001), increased production of plasminogen activator inhibitor-1 (Pelletier et al., 1997) as well as the induction and activity of COX-2 (Di Battista et al., 2001; Fahmi et al., 2001). Nimesulide reverses the inhibitory effects of interleukin-1 on cartilage proteoglycan synthesis, as well as inhibiting interleukin-1 induced production of oxyradicals by cartilage and nitric oxide by chondrocytes (Rainsford et al., 2002). Overall, the results from these various biochemical studies suggest that nimesulide might have a role in the protection of cartilage degradation in arthritic disease (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), in contrast with other NSAIDs some of which may accelerate this degradation process (Rainsford et al., 1992, Walker and Rainsford, 1997). The therapeutic significance of these observations can be seen in clinical studies in which therapeutic doses of nimesulide, but not ibuprofen, showed to significantly decrease the serum levels of MMP's (Fig. 8), including stromelysin (or matrix metalloprotease-3, MMP-3) (Kullick et al., 2002; Kalajdzic et al., 2002; Bevilacqua et al., 2004), which may be related to

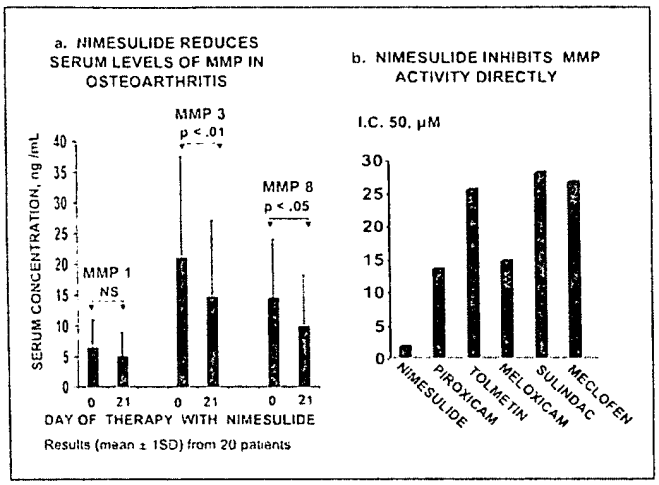

Fig. 8. Actions of nimesulide in reducing levels of metallo-proteinases (MMP's) in the serum of patients with osteoarthritis that had taken nimesulide [a], and of MMP enzymatic activity *in vitro* [b].
a. Based on data from Kullich et al. (2002)
b. Based on data from Barracchini et al. (1998)

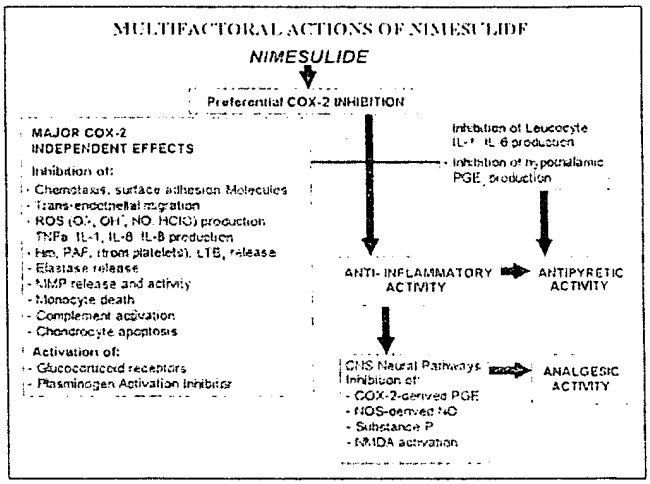

Fig. 9. Summary of the multi-factorial actions of nimesulide involving prostaglandin-related, and non-prostaglandin-related effects.
Abbreviations: COX-2, cyclo-oxygenase-2, TNFα, tumour necrosis factor-α, Hm, histamine, PAF, platelet activating factor, ROS, reactive oxygen species, MMP, metalloproteinase(s)

reduction in the serum levels of hyaluronan (Bevilacqua et al., 2004), and the C-terminal cross-linking telopeptide of collagen II (Kalajdzic et al., 2002) both biomarkers which predicts a poor outcome of the osteoarthritis joint disease.

A recent observation by the Pelletier group concerning the effect of nimesulide in activating the glucocorticoid receptor and so producing inhibition of the transcription of COX-2 (DiBattista et al., 2001; Fahmi et al., 2001), so inhibiting the translation of the mRNAs for MMP's and pro-inflammatory cytokines (Pelletier et al., 1999). This may represent a novel and far-reaching action of the drug not seen with other NSAIDs. Further studies are, however, needed to confirm the effects of nimesulide on glucocorticoid receptor activation coincident with reduction in expression of the mRNA for proteins regulating production of the abovementioned inflammatory mediators.

In conclusion, nimesulide has a range of multi-factorial actions *in vitro*, some of which have been demonstrated *ex vivo* or *in vivo* in patients (Bennett and Villa, 2000; Bennett, 2001); these effects are summarised in Figure 9. Many of these are most likely related to core effects in causing inhibition of the production and actions of COX-2, cyclic AMP and glucocorticoid receptors, which appear to underlie the anti-inflammatory activity of nimesulide. The preferential inhibitory effects on COX-2, *ex vivo* inhibition of phagocytosis (as an effect related to ROS) and levels of serum MMP-3 and MMP-8 are actions of the drug that have been shown in humans. In models of inflammation in rats, nimesulide has been found to reduce PGE_2, TNF_α and neutrophil accumulation in inflammatory exudates thus providing further support for the multi-factorial actions *in vivo*. These multiple actions of the drug mean that the expression of anti-inflammatory activity is a consequence of regulation of the production and actions of a wide range of mediators of inflammation in contrast to the sole dependence of effects on production of prostaglandins from COX-2 activity as observed with NSAIDs such as the coxibs.

Analgesic Activity

The analgesic activity of nimesulide is partly due to the capability of reducing the activity of the CNS nociceptive system with an onset of action consistent with the pharmacokinetic characteristics of the drug (Rainsford et al., 2005). The well-established increase in prostaglandins in the central nervous system (CNS) during pain transmission is due to induction and activity of COX-2 (Yamamoto and Nozaki-Taguchi, 1996; Ohtori et al., 2004; Veiga et al., 2004; Hofacker et al., 2005), although there is some evidence that COX-1 may also be involved (Zhu et al., 2003). Furthermore, nitric oxide (NO) plays a significant role including mediating sensitisation in the transmission of pain in the CNS (Schulte et al., 2003; Schmidtko et al., 2003; Tassorelli et al., 2004). Its presence and sustained elevation is critical in maintaining central sensitisation whilst the inhibition of NOS as well as COX-2 reduces central sensitisation in pain models. Experimental studies in animal models have demonstrated that nimesulide inhibits COX-2 and nitric oxide synthases (NOS) in the spinal cord (Tassorelli et al., 2003) confirming the central action of the drug in humans (Sandrini et al., 2001, 2002).

Figure 10 shows the possible modes of action of nimesulide at the level of the dorsal horn which may represent a key region of the central nervous system affected by the drug. That central actions of nimesulide are important in control of spinal neurotransmission in humans is illustrated from the study shown in Figure 11 (Sandrini et al., 2001).

Some of the mechanisms of the analgesic actions of nimesulide that have been shown in experimental models require more extensive investigations in humans to establish the clinical significance of these actions. However, as nimesulide affects a considerable number of mediators involved in both peripheral and central nervous system mediation of pain relief in hyperalgesia (Rainsford et al., 2005).

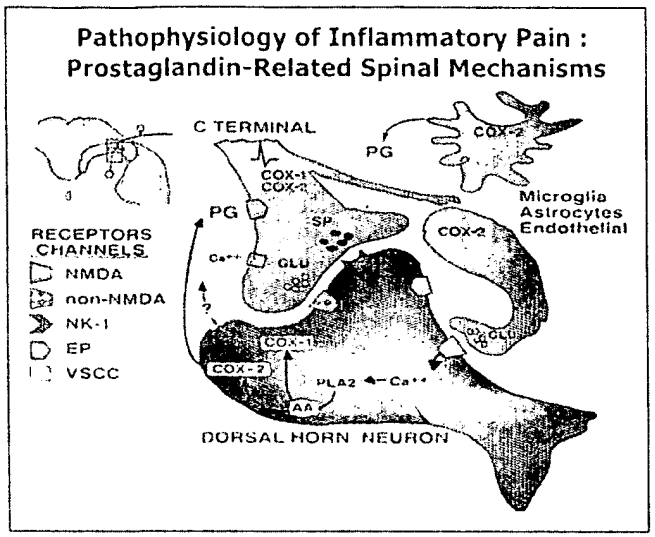

Fig. 10. Pathways involving prostaglandins (principally PGE_2) derived from cyclo-oxygenases 1 and 2 and their actions in mediating hyperalgesic responses to inflammatory pain in the dorsal horn. Induction of COX-2 during painful stimuli amplifies the production of PGE_2 and with this the stimulation of nerves impinging on and mediated from the dorsal horn via afferent nerves in the spinothalamic tracts of the central nervous system. PGE_2 production from activation of dorsal horn neurones by afferent inputs from C- and Aδ-fibres causes (a) release of glutamate which acts on NMDA and non-NMDA receptors, and (b) release of substance P which acts on neurokinin-1 receptors (NK-1). The activation of these receptors leads to increased flux of Ca^{++} ions that activate phospholipase-A_2 which in turn hydrolyzes phospholipids and release of arachidonic acid which serves as a substrate for COX-1 and COX-2.
Nitric oxide synthase of the neuronal type, nNOS, is also activated and the nitric oxide produced during neural stimulation contributes to the activation of afferent pathways.
Nimesulide inhibits release of PGE_2 and NO and so modulates neural transmission at the level of the dorsal horn. Whether sufficient concentration of the drug reach the dorsal horn to block COX-1 is not known. PGE_2 production from accessory cells (e.g. microglia, astrocytes) and endothelial cells also contributes to the cycle of activation of dorsal horn cells. From Bianchi et al. (2005); unpublished figure.

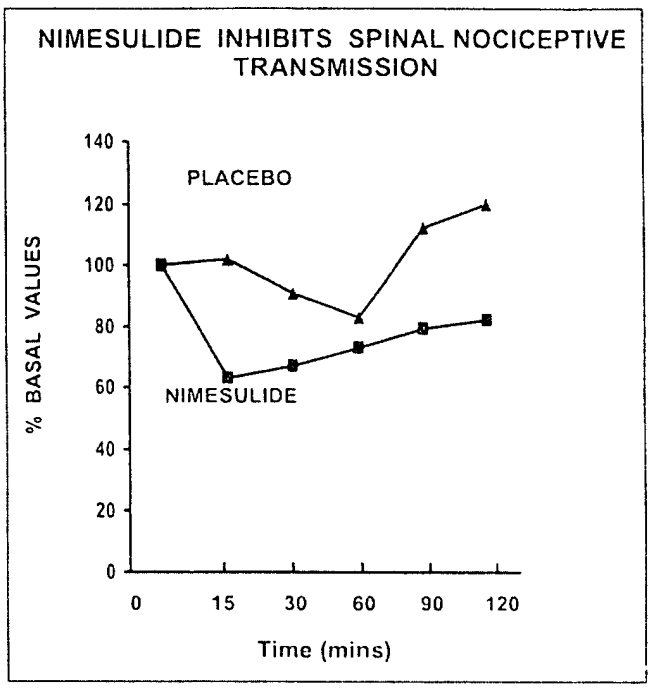

Fig. 11. Effects of nimesulide compared with placebo on spinal nociceptive transmission in human volunteers. From Sandrini et al. (2001).

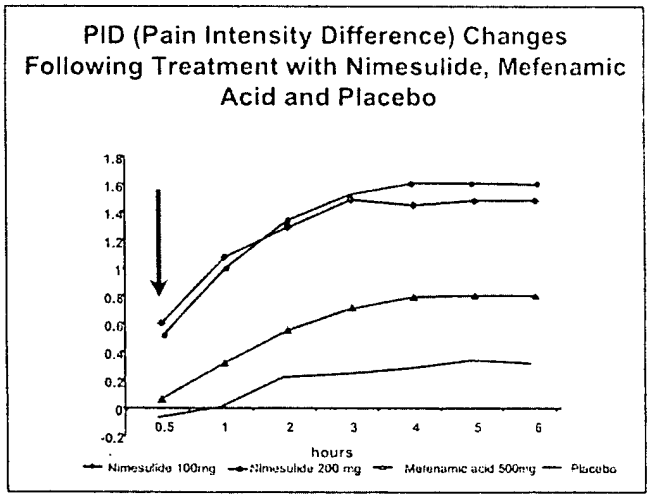

Fig. 12. Pain Intensity Difference (PID) Scores following dental surgery over a 6 h period following oral ingestion of 100 or 200 mg nimesulide compared with a comparable analgesic/anti-inflammatory dose of mefenamic acid and showing superior effects of both these NSAIDs over placebo.
The dental surgery pain model is one of the frequently used human pain models which are very responsive to NSAIDs and analgesics. The effects of NSAIDs have been found to relate to inhibition of PGE_2, substance P and other mediators of acute inflammation.
From Ragot et al. (1994).

The fast onset of pain relief which is evident 15 min after oral intake of the drug is evident from studies in human volunteers where the spinal nociceptive transmission was determined after intake of nimesulide compared with placebo (Fig. 11) (Sandrini et al., 2001, 2002). These observations are paralleled in humans by the reduction of pain from ingestion of nimesulide which was apparent after 15 min from the administration, with a statistically significant superior onset of action being apparent versus the comparator drugs (Fig. 12) (Bianchi and Broggini, 2002).

In addition to affecting production of spinal PGE_2 nimesulide appears to influence the actions of NO in neural transmission (Sandrini et al., 2002). Undoubtedly, the rapid onset of analgesia by nimesulide is linked to the pharmacokinetic properties of the drug. Thus, after oral administration of 50 to 200 mg nimesulide tablets to healthy volunteers, plasma C_{max} values, ranging from 2.0 to 9.9 mg/L, are achieved quite rapidly within 1.7 to 3.2 h (Bernareggi, 1998). Studies in rheumatic patients have shown that relatively high nimesulide concentrations are present in inflamed synovial tissues and at earlier times than plasma peak times (Ligniere et al., 1990). The rapid accumulation in synovial fluids is also accompanied by rapid reduction in synovial fluid concentrations of PGE_2 (Duffy et al., 2003), thus indicating the synovial fluid pharmacodynamics of nimesulide coincides with the expression of pharmacological actions of the drug.

There is, however, evidence of reduced bio-equivalence of some copy and generic versions of nimesulide that can affect the pharmacokinetics of the drug compared with that of the original formulation of nimesulide (e.g. Aulin®) (Maroni and Gazzaniga, 2005. Any reduction in bioavailability of nimesulide would be expected to result in lower efficacy. A gel formulation of nimesulide has been found to have pharmacokinetic properties like that of diclofenac gel with comparable absorptive properties that favour local application to inflamed tissues and joints (Sengupta et al., 1998; Bianchi et al., 2005).

Clinical Applications

Over 200 clinical trials have been conducted in more than 90.000 patients with nimesulide in a variety of acute and chronic inflammatory and painful conditions (Ward and Brogden, 1988; Rabasseda, 1996; *Anonymous*, 1998; Bianchi et al., 2005).

1. Acute pain

The rapid onset of action of nimesulide is particularly evident in a variety of painful conditions where acute inflammation is the most predominant component. Thus, nimesulide has been shown to consistently reduce pain and where studied the inflammatory reactions and found to be superior to placebo and comparable or in some cases better that reference NSAIDs in (a) the treatment of soft tissue injuries and extra-articular trauma (where the gel formulation also gives good pain relief) (Ward and Brogden, 1988; Calligaris et al., 1993; Dreiser and Riebenfeld 1993a, 1993b; Lecomte et al., 1994; Jenoure et al., 1998; Dhaon et al., 1998, 2000), (b) various ear, nose and throat (ENT) inflammatory conditions (e.g. otitis, sore throat) (Milvio, 1984; Bianchini et al., 1993; Ottavani et al., 1993), (c) dental surgery (Cornaro, 1983; Ferrari Parabita et al., 1993; Pierleoni et al., 1993; Ragot et al., 1993, 1994; Scolari et al, 1999; Bracco et al., 2004), (d) odonto-stomatological pain (Salvato et al., 1984; Bucci et al., 1987; Moniaci et al., 1988) and (e) a range of post-operative conditions (Stefanoni et al., 1990; Ramella et al., 1993; Binning, 2004). In the dental pain model nimesulide demonstrates rapid onset of action and is more potent than comparable doses of mefenamic acid and placebo (Fig. 12) (Ragot et al., 1994). In this model it is of interest to note that the pain relief (measured as Pain Intensity Difference (PID) Scores were the same over the time interval up to 6hrs following 100 mg compared with 200 mg nimesulide, suggesting there the 100 mg dose is adequate (Pierleoni et al., 1993). These observations can be related to the non-linear plasma kinetics of the drug which deviates above 100 mg dosage (Bernareggi, 1998).

In all the studies involving investigation of acute pain nimesulide has been as effective as effective as the most widely used NSAIDs (e.g. naproxen, ibuprofen, diclofenac, mefenamic acid and celecoxib and rofecoxib) where it frequently showed superior or similar efficacy but with evidence of a better GI tolerability (Bianchi and Broggini, 2002, 2003).

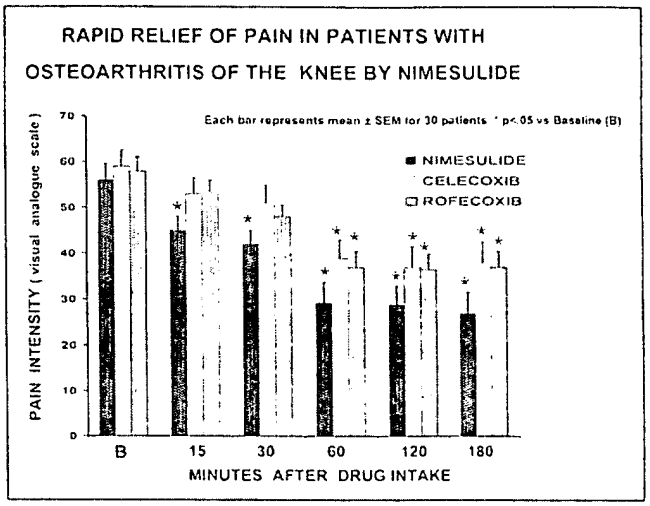

Fig. 13. Onset of pain relief in knee osteoarthritis from oral nimesulide compared with celecoxib and rofecoxib.
From Bianchi and Broggini (2003).

2. Pain and Joint Inflammation in Osteoarthritis

NSAIDs are among the mostly widely-used drugs for the symptomatic treatment of painful osteoarthritis (Kean and Buchanan, 2005). The recommendations for therapy of pain and joint inflammation in this condition by the American College of Rheumatology, Subcommittee on Osteoarthritis Guidelines in 2000 (Kean and Buchanan, 2005) state that:

1. Paracetamol may give pain relief in mild osteoarthritis, but NSAIDs are more effective.
2. NSAIDs are superior to paracetamol in more severe osteoarthritis.
3. Paracetamol can be dangerous in patients with a history or current alcohol abuse or other liver injury.
4. Paracetamol can (in high doses) cause GI bleeds and ulcers.

Thus, NSAIDs are considered as a valid alternative to the first choice treatment, paracetamol, with particular reference to flares up when the first choice treatment may result inadequate. The critical point is to choose an NSAID with a low GI risk. This is where nimesulide has a place in therapy of osteoarthritis.

As noted earlier nimesulide has been found to have relatively rapid onset of analgesic action in hyperalgesia in humans when compared with well-established NSAIDs such as diclofenac and the two coxibs, celecoxib and rofecoxib (Bianchi and Broggini, 2002). In osteoarthritis, nimesulide also has a rapid onset of analgesia in comparison with the celecoxib and rofecoxib (Fig. 13) (Bianchi and Broggini, 2003).

In addition to producing rapid pain relief, the action of nimesulide in arthritic joints such as the inhibitory activity on COX-2 and NO activity, the prevention of cytokine–induced cartilage degradation compared with other NSAIDs, the oxyradical-scavenging activity, and inhibitory effects on apoptosis give a credible basis for the use of nimesulide in osteoarthritis (OA) and other musculoskeletal joint diseases and trauma states in relation to effects on joint functions (Rainsford et al., 2002, 2005; Bianchi et al., 2005). Aside from this

pharmacological rationale there is also a large amount of data on the clinical effectiveness of nimesulide have been obtained from studies in a variety of experimental designs, among them placebo-controlled and double blind studies and large-scale including post-marketing evaluations (Fossaluzza and Montagnani, 1989; Pochobradsky et al., 1991; Blardi et al., 1992; Dreiser and Riebenfeld 1993b; Estevez et al., 1993; Bourgeois et al., 1994; Lucker et al., 1994; Quattrini and Paladin, 1995; Porto et al., 1998; Roy et al., 1999; Sharma et al., 1999; Huskisson et al., 1999; Zgradic, 1999; Kriegel et al., 2001; Fioravanti et al., 2002; Bianchi and Broggini, 2003; Herrera and Gonzales, 2003; Omololu et al., 2005; Bianchi et al., 2005).

In these studies nimesulide significantly reduced the signs and symptoms of OA with an efficacy at least comparable to the reference drugs, including etodolac (Lucker et al., 1994), diclofenac (Estevez et al., 1993; Porto et al., 1998; Huskison et al., 1999; Zgradic, 1999; Omololu et al., 2005), ketoprofen (Dreiser and Riebenfeld, 1993b), naproxen (Fossaluzza and Montagnani, 1989; Quattrini and Paladin, 1995; Kriegel et al., 2001; Fioravanti et al., 2002), piroxicam (Drieser and Riebenfeld, 1993b; Sharma et al., 1999) as well as the coxibs, celecoxib (Bianchi and Broggini, 2003) and rofecoxib (Bianchi and Broggini, 2003; Bourgeois et al., 1994)). Of particular importance is that several studies (Blardi et al., 1992; Bourgeois et al., 1994; Porto et al., 1998; Wober, 1999) have shown the relative safety of the drug, especially in relation to the gastrointestinal tract (Porto et al., 1998) and economic advantages (Liaropoulos, 1999; Tarricone et al., 2001) of nimesulide in the treatment of osteoarthritis as well as other musculo-skeletal conditions (Wober, 1999; Pohjolainen et al., 2000).

3. Primary Dysmenorrhoea

The use of NSAIDs in the treating primary dysmenorrhoea is particularly indicated as this painful condition is directly linked to modification in prostaglandin production and affects over 50% of all menstruating women (Ylikorkala and Dawood, 1978; Jamieson and Steege, 1996; Harlow and Park, 1996; Smith, 1997; Coco, 1999). NSAIDs are well established therapies for the relief of menstrual cramps and other symptoms of primary dysmenorrhoea (Coco, 1999; Dawood, 1988, 1993; Stones and Mountfield, 2000). In a number of studies nimesulide has been found to reduce pain and menstrual symptoms (Moggian et al., 1986; Pulkkinen, 1987, 2001; Lopez Rosales et al., 1989; Pulkkinen et al., 1992; Pirhonen et al., 1995; Melis et al.,1997; Facchinetti et al., 2001). Moreover, studies in more than 1400 women, over 1000 of which treated with nimesulide, widely document the activity of nimesulide in decreasing the intrauterine pressure, Doppler assessment of arterial blood flow and the reduction of $PGF_{2\alpha}$; the latter plays a key role in the pain perception (Pulkkinen, 1987; Pulkkinen, et al, 1992; Pirhonen and Pulkkinen, 1995). Rapid onset of pain relief was observed with nimesulide in comparison with other NSAIDs, e.g. diclofenac (Facchinetti et al., 2001).

4. Headache, ENT Infections, Fever and Minor Pain States

Like other NSAIDs (Rainsford, 2004b) nimesulide has well documented evidence for relieving symptoms associated with migrainous and non-migraine headaches, upper respiratory tract, ear nose and throat infections with associated fever, as well as in minor pain states (Reiner and Massers, 1984; Reiner et al., 1985; Antonelli et al., 1993; Cunietti et al., 1993; Giacovazzo et al., 1993; Zuckermann et al., 1993; Goyal et al., 1998; Neimark et al., 2004) (also reviewed in Bianchi et al., 2005). A particular advantage in the respiratory conditions is the relatively low likelihood of asthmatic and other allergic reactions with nimesulide (Bianco et al., 1993, Senna et al., 1996; Bianchi et al., 2005).

5. Cancer Pain

NSAIDs represent the first step in the World Health Organization guideless for stepwise analgesia in cancer pain (Rainsford, 2004b) Nimesulide has been shown to have analgesic activity in various cancer pain states, with activity that is comparable with that of established NSAIDs such as diclofenac and naproxen (Ventafridda et al., 1990; Gallucci et al., 1992; Corli et al., 1993; Toscani et al., 1993). Of particular value is the use of the suppository formulation of nimesulide which as shown in a study by Corli et al. (1993) to have a rapid onset and sustained pain relief.

There is much interest in the potential for NSAIDs to prevent the development of cancer (Ulrich et al., 2006). Recent studies in experimental models suggest that nimesulide may have the potential for cancer chemoprevention in colorectal and lung cancers (Rainsford, 2005a), head and neck cancer (Lin et al., 2002) and from topical application in oral cancers (Sood et al., 2005). There are multiple actions of nimesulide on cancer cells including its inhibitory effects on COX-2 activity, signal transduction pathways, angiogenesis and selective activation of apoptosis that may be implicated in arresting cancer cell growth and prevention of the spread of tumours (Rainsford, 2005a). A recent report indicated that nimesulide nimesulide has inhibitory effects on oestrogen metabolism by aromatase activity in breast cancer cells which may have significance for prevention of breast cancer (Brueggemeier et al., 2005).

5. Conclusions

The extensive studies and over 20 years of successful clinical use of nimesulide in treating musculo-skeletal and acute and chronic pain states has shown the drug exhibits rapid and sustained control of inflammation and pain.

Adverse Reactions and Relative Safety

Several reviews have been published in recent years on the adverse reaction profile of nimesulide in comparison with that of other NSAIDs (Rainsford, 1996, 1998, 1999b, 2001; Bianco et al., 1993; Senna et al., 1996; Conforti et al., 2001; Lanas 2001; Boelsterli, 2002a, 2000b; Traversa et al., 2003; Laporte et al., 2004). These studies show that nimesulide has, overall, a pattern of organ reactions similar to that from other NSAIDs, though there are quantitative differences in the incidence of adverse reactions.

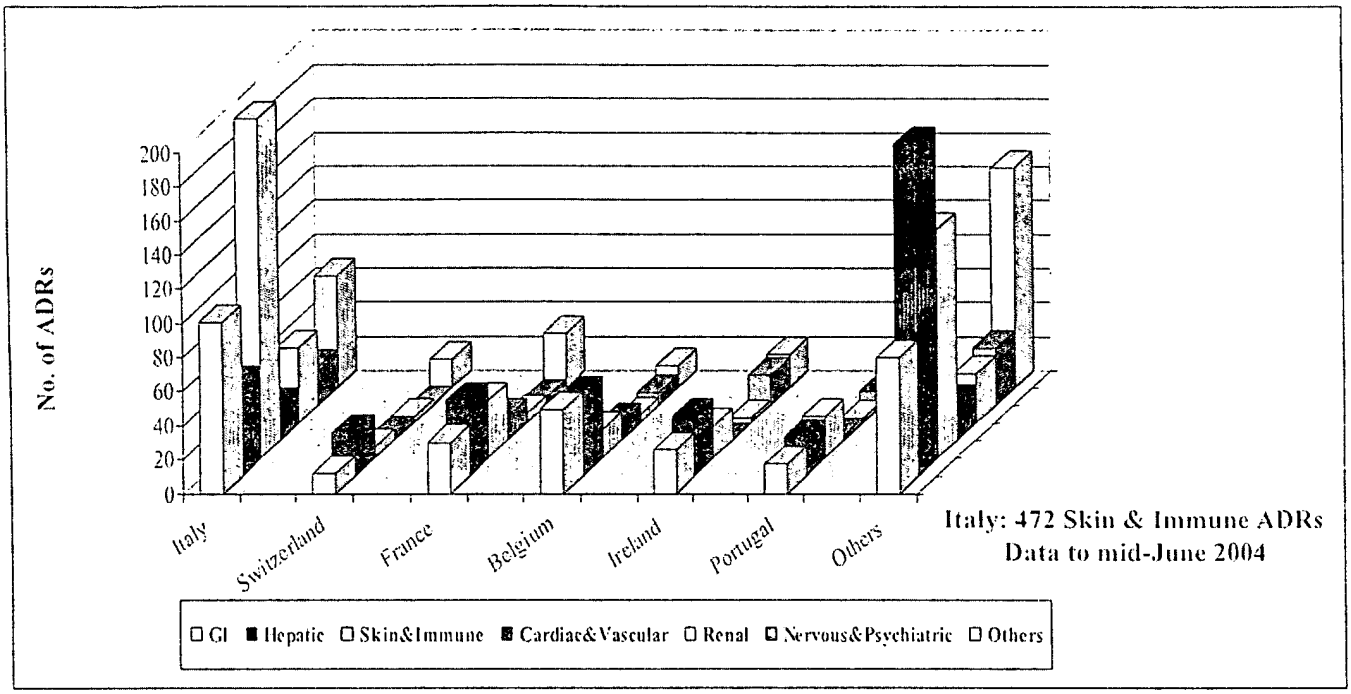

Fig. 14. Adverse Drug Reactions (ADRs), both serious and non-serious, from nimesulide by body system reported in the main countries where this drug has been marketed. From Bjarnason et al. (2005).

A comprehensive review was recently undertaken by Bjarnason and co-workers (2005) of all aspects of the relative safety and the mechanisms that are understood to underlie the adverse reactions from nimesulide. The data reviewed was derived from (a) epidemiological studies, (b) spontaneous reports of adverse drug reactions (ADRs) reported to Helsinn Healthcare SA, the WHO Nimbus Database and in published reports, (c) controlled clinical investigations in human volunteers and patients, (d) studies in laboratory animal models *in vivo* involving conventional toxicological and bioassays or pharmacological investigations designed to establish mode of action in relation to known adverse events (e.g. gastric acid secretion, parameters of renal function), and (e) *in vitro* studies in cellular or tissue systems, molecular biological and biochemical and molecular studies investigating mechanisms of toxic reactions or physiological functions in target organs wherein adverse events are known to occur. Detailed review of these investigations is found in Bjarnason et al. (2005) to which the reader is referred. Here the principal observations of the adverse reactions and toxic effects in the major organ systems are summarized thus:

(1) Overall pattern of adverse reactions

Figure 14 shows the overall pattern of serious adverse reactions in the main countries where nimesulide has been marketed by Helsinn Healthcare SA since the introduction of the drug in 1985. The majority of reactions have been in the skin and immune systems with fewer being evident in the GI, hepatic and renal systems; this is at variance with the pattern observed with classical NSAIDs, where ADRs in the GI system usually predominate (Rainsford and Velo 1984, 1985; Rainsford, 1996, 1998, 1999a, 2001; McGettigan et al., 2000; Lanas, 2001; Laporte et al., 2004).

(2) Gastrointestinal tract:

Serious GI events from nimesulide are rare: in the past 5 years these have averaged 1.1 cases per 10^6 treatment courses (Bjarnason et al., 2005). Serious GI ADRs comprise 15.7% of all reports of which 4.4% were fatal but possibly not due to the drug. Pharmaco-epidemiological studies in case-control, cohort or hospitalization studies have given risk assessments (Relative Risk or Odds Ratios) of 1.2, 2.0 and 4.0 respectively with reference drugs excepting ibuprofen (for which the values are comparable) exceeding these by 2–5 fold.

Gastro-duodenal endoscopy and intestinal permeability studies have shown that nimesulide 100 mg b.i.d. produces little if any GI damage (Bjarnason and Thjodleifson, 1999). This contrasts with naproxen 500 mg b.i.d. or other conventional NSAIDs, which all produce visual evidence of gastroduodenal damage and with the former increased intestinal permeability and inflammation. As noted earlier in the section on pharmacological studies these low GI effects of nimesulide can be related to sparing of gastric mucosal and plasma COX-1 combined with its properties of controlling histamine release from mast cells, apparent anti-acid secretory activity, inhibitory effects on leucocyte emigration and activation, antioxidant activity and possibly effects on the production and actions of proinflammatory cytokines. Data from studies in experimental animal models strongly

supports the epidemiological data showing that nimesulide has a relatively low risk of serious GI reactions especially in comparison with other NSAIDs.

(2) Hepatic

Hepato-biliary disorders associated with nimesulide account for 14.3% of all serious ADRs, while abnormal laboratory findings comprise 6.6% of these, principally abnormal liver function tests. Like other NSAIDs, nimesulide is infrequently associated with elevation of the liver transaminases (ALT, AST, γ-GT), and less so with liver function tests (ALP, free and conjugated bilirubin) and, rarely, cholestatic jaundice. In most cases cessation of the drug results in restoration to normal of elevated liver transaminases and liver function tests (Bjarnason et al., 2005).

In pharmaco-epidemiological studies (Traversa et al., 2003) the occurrence of hepatopathy from nimesulide is at the upper end of the range compared with NSAIDs. The relative risks are in the range of 1.3–1.4. Most cases have confounding factors (other hepatotoxic drugs or liver diseases) (Rainsford, 1998, 1999b; Boelsterli et al., 2002a, 2002b). High concentrations (up to 100 μmol/L) of nimesulide, its metabolites and manufacturing impurities have not been found to cause direct cytotoxic damage to liver cells in culture (Rainsford et al., 2001), although increased cell damage is evident when paracetamol or other hepatotoxic drugs are present (K D Rainsford, unpublished studies). Thus it is unlikely that the drug or its metabolites have direct actions on liver cells. It is possible that the liver reactions attributed to nimesulide are idiosyncratic (Boelsterli, 2002b). Considerable evidence exists to show that most liver ADRs have been in patients that have taken hepatoxic drugs and/or have liver diseases.

The formation of nitroso or hydroxylamine reactive metabolites of nimesulide has been suggested to be responsible for the liver damage from the drug (Boelsterli, 2002b), like that of reactive metabolite injury from diclofenac, paracetamol and other hepatotoxins (Boelsterli, 2002a). There is no evidence to support this reactive metabolite hypothesis of cell injury by nimesulide. Reduction in mitochondrial ATP and other functions has been observed with nimesulide following administration of high doses of the drug to rats. This phenomenon is related to uncoupling of oxidative phosphorylation like that observed with acidic NSAIDs and might account for the development of liver injury by these drugs. Reduction in ATP may initiate apoptosis by these drugs.

(3) Renal

Renal and urinary tract disorders comprise 4.7% of all ADRs reported and are rare. These resemble those encountered with other NSAIDs (Bjarnason et al., 2005) They include tubular and interstitial nephritis, nephritic syndrome and renal failure.

Inhibition of renal prostaglandin production accounts for the transient physio-pathological renal effects of the drug on electrolyte balance, water impairement, and renin production; these being similar to those of other NSAIDs. Renal ADRs that appear in the elderly are related to impaired renal clearance of the drug.

(4) Cutaneous and allergic reactions

Nimesulide is frequently associated with minor skin reactions (erythematous rashes, uricaria etc); these being akin to those with other NSAIDs (Rainsford, 1992) Stevens-Johnson and Lyell's syndromes have been rarely reported; the occurrence of these reactions may be lower than observed with other NSAIDs. Intolerance to nimesulide is rare in patients with pseudo-allergic reactions to other NSAID and aspirin-sensitive asthmatic patients (Bianco et al., 1993; Senna et al., 1996).

(5) Cardiovascular system

Serious cardiovascular reactions (myocardial infarction, congestive heart failure) are rare with nimesulide (EMEA, 2005a, 2005b) and do not appear as frequent as observed with coxibs (US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b). Mild blood pressure changes have been observed with nimesulide (Rainsford, 1999) and this is also observed with most NSAIDs and could be related to COX-2 inhibition (Khanna et al., 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b).

(6) Role of Pharmacokinetics

The role of pharmacokinetics of nimesulide in determining adverse reactions and toxicity has been reviewed (Rainsford, 1999b; Bernareggi and Rainsford, 2005). The likelihood of drug accumulation upon repeated dosage (i.e. after steady state levels of the drug have been achieved at 7 days) in elderly patients without hepato-renal conditions is rare. As shown in Figure 18 the clearance and volume of distribution of nimesulide is unaffected by age. Furthermore, there are no differences in pharmacokinetic parameters between the sexes (Fig. 19) (Bernareggi and Rainsford, 2005) such as observed with some NSAIDs (e.g. the salicylates (Rainsford, 1996, 2004). Of the drug interactions those affecting pharmacokinetics include the reduction by nimesulide in the bioavailability of furosemide when taken with nimesulide concomitant with reduction in the natriuretic and, to a lesser extent, the kaliuretic effects of this drug (Bernareggi and Rainsford, 2005). The pharmacokinetics of warfarin, digoxin (in patients with mild congestive heart disease), theophylline and glybencamide are mostly unaffected by nimesulide and *vice versa* (Bernareggi and Rainsford, 2005). Prothrombin times during treatment with warfarin or acenocoumarol are unaffected by nimesulide (Rainsford, 1999b). Reduced plasma levels of theophylline have, however, been found in

patients with chronic obstructive lung disease that received nimesulide (Rainsford, 1999b). Cimetidine and antacids do not affect the bioavailability of nimesulide (Bernareggi and Rainsford, 2005) possibly because the ionisation of the drug in the stomach is not an issue for its absorption. Some drugs affect the protein binding of nimesulide but probably these are not sufficient to be of clinical significance. These observations suggest that there are few significant drug interactions between nimesulide and other drugs that may be taken by patients with osteoarthritis or other musculo-skeletal conditions.

Benefit/risk profile

Based on what has been discussed above the following conclusions can be drawn on the overall benefit/risk profile of nimesulide.

The therapeutic benefits of nimesulide have been compared with both placebo and the most widely used NSAIDs for the main approved indications, including acute pain, treatment of painful osteoarthritis and primary dysmenorrhoea. Nimesulide proved to be a valid alternative to other NSAIDs, with a similar or even superior clinical efficacy characterized by a fast onset of action.

As evident in the safety section, nimesulide shares the characteristic side effects of NSAIDs, such as GI, skin, renal, hepatic reactions. Like other drugs in the class, the occurrence of adverse reactions suggesting hypersensitivity comprises a significant proportion of the total reactions. Analysis of the incidence of all adverse reactions from the available data confirms this to be in line with the class. In particular it can be affirmed that the incidence of upper GI perforation, bleeding and ulceration is low and that nimesulide is probably less prone to produce gastrointestinal bleeding than other NSAIDs. Incidence rate is similarly low for renal, serious skin and hepatic reactions.

Data on post marketing surveillance confirms that there is not signal of any changes in the clinical characteristics of listed serious and non-serious adverse reactions overtime or of any potentially 'new' adverse reactions or new signals related to nimesulide. This, together with the evidence from clinical studies, allows confirming that the favourable and invariant benefit risk profile of nimesulide.

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